NICE National Institute for Health and Care Excellence

NICE guidance

Guidance on the use of drugs for early thrombolysis in the treatment of acute myocardial infarction

Technology appraisal guidance
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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

This guidance provides recommendations on the selection of thrombolytic drugs in patients with acute myocardial infarction (AMI). Recommendations are made in relation to the use of the drugs in hospital and pre-hospital settings. The guidance does not compare hospital and pre-hospital models of delivering thrombolysis.

1.1 It is recommended that, in hospital, the choice of thrombolytic drug (alteplase, reteplase, streptokinase or tenecteplase) should take account of:

- the likely balance of benefit and harm (for example, stroke) to which each of the thrombolytic agents would expose the individual patient
- current UK clinical practice, in which it is accepted that patients who have previously received streptokinase should not be treated with it again
- the hospital's arrangements for reducing delays in the administration of thrombolysis.

1.2 Where pre-hospital delivery of thrombolytic drugs is considered a beneficial approach as part of an emergency-care pathway for AMI (for example, because of population geography or the accessibility of acute hospital facilities), the practicalities of administering thrombolytic drugs in pre-hospital settings mean that the bolus drugs (reteplase or tenecteplase) are recommended as the preferred option.

2 Clinical need and practice

2.1 Acute myocardial infarction (AMI) is caused by blockage of a coronary artery by a thrombus or clot. This is usually the result of rupture of an atherosclerotic plaque within the artery. The heart muscle supplied by that artery is damaged or dies because of lack of oxygen (ischaemia). Patients with AMI may develop heart failure or potentially fatal cardiac arrhythmias as a result of damage to the heart muscle. These and other complications may occur early, within the first few hours of the event, or may develop over the subsequent months or years.

2.2 Around 240,000 people experience AMI in England and Wales each year. Up to 50% of people who have an AMI die within 30 days of the event, and over half of these deaths occur before medical assistance arrives or the patient reaches hospital.

2.3 Onset of AMI symptoms is usually rapid and the highest risk of death (usually as the result of an acute fatal arrhythmia) is within the first hour of experiencing symptoms – around one-third of all AMI deaths occur within the first hour.

2.4 Thrombolytic drugs break down the thrombus so that the blood flow to the heart muscle can be restored to prevent further damage and assist healing. The sooner the blood flow can be restored, the better the chances of avoiding the death of the heart muscle. Along with clinical symptoms (typically but not exclusively chest pain), characteristic changes in the 12-lead electrocardiogram (ST segment elevation) provide the most immediate indication of the diagnosis of AMI for patients requiring thrombolysis for AMI.

2.5 Intravenous thrombolytic therapy is an established standard treatment for AMI. It is estimated that around 50,000 patients currently receive thrombolysis in England and Wales each year. However, evidence suggests that thrombolysis continues to be under-used.

2.6 Thrombolytic drugs are routinely given in hospital as soon as possible after a confirmed diagnosis of AMI. Additionally, their administration in pre-hospital settings, principally by ambulance paramedics, is becoming more common.

2.7 Early primary percutaneous coronary intervention (PCI) may be an alternative to thrombolysis. Despite research evidence of the potential value of early PCI, currently few hospital trusts have the capacity to provide it. Treatment delivering thrombolytics in combination with glycoprotein IIb/IIIa inhibitors is also the subject of research studies. However, these interventions are beyond the scope of this appraisal.

3 The technology

3.1 Thrombolytic drugs

3.1.1 In the UK, four thrombolytic agents are licensed and available to treat AMI. All act by promoting the activity of circulating plasminogen. There is a long history of use of one, streptokinase, whereas the other three, alteplase, reteplase and tenecteplase, are newer options. Streptokinase is derived from streptococcal bacteria. Streptokinase is given by intravenous (IV) infusion. Alteplase was introduced in the late 1980s. It is essentially the same as the naturally occurring activator of plasminogen in the human body, and is produced by recombinant DNA technology. It is given by IV infusion. Reteplase and tenecteplase have been introduced more recently (1997 and 2001, respectively). They are new modified forms of plasminogen activator and can be given by rapid IV bolus injection, rather than infusion.

3.1.2 The timing of administration is a crucial factor determining the extent of benefit achieved by thrombolysis, and treatment should ideally be given as soon as possible (normally up to 12 hours) after the onset of AMI symptoms.

3.1.3 Bleeding complications are the main risks associated with thrombolysis. The most important bleeding complication is haemorrhagic stroke, which occurs in 0.5% to 1.0% of patients and is associated with high mortality and long-term disability in survivors. Bleeding may occur at the injection site, in the gastrointestinal tract or elsewhere. Hypotension may also occur. The risks and benefits of giving thrombolysis need to be considered in individual patients and settings. The risk of haemorrhagic stroke following thrombolysis increases with age and blood pressure. Thrombolysis is contraindicated in individuals with bleeding disorders or a history of recent haemorrhage, trauma, surgery or acute cerebrovascular event. For full details of side effects and contraindications, see the Summary of Product Characteristics for the individual agents.

3.1.4 Heparin (an anticoagulant) is given with all of the thrombolytic drugs except streptokinase. It is usually administered as an IV bolus injection before thrombolysis, followed by an IV infusion. When given with tenecteplase the

heparin dose is weight adjusted. Aspirin (an antiplatelet agent) is also usually given with any thrombolytic drug, because it delivers a mortality benefit in its own right.

3.1.5 Streptokinase (Streptase) is indicated up to 12 hours after onset of symptoms. It is administered as an IV infusion over 1 hour. It has been extensively studied and remains widely used. Streptokinase is associated with hypotension, infrequent allergic reactions and, rarely, anaphylaxis. Patients treated with streptokinase develop anti-streptococcal antibodies, which can inactivate the drug if subsequent treatment is needed. Consequently in current UK practice, patients are usually treated with streptokinase only once. It is estimated that around one-third of people with AMI have contraindications to streptokinase. A recent survey found that 82% of hospitals in England use streptokinase for eligible patients experiencing their first AMI; other data suggest that streptokinase represents between 53% and 65% of thrombolytic drug use. Streptokinase costs £80 to £90 per patient (excluding VAT; BNF 43, March 2002).

3.1.6 Alteplase (Actilyse, recombinant human tissue plasminogen activator, rtPA) can be delivered in a standard or accelerated regimen. The accelerated regimen, which is much more commonly used, is indicated up to 6 hours after symptom onset and is delivered by an initial IV bolus injection, followed by two IV infusions, the first given over 30 minutes and the second over 60 minutes. The standard regimen is indicated between 6 and 12 hours after symptom onset and requires a bolus injection followed by five infusions over 3 hours. Like the other newer drugs, alteplase does not stimulate the production of antibodies, so it can be used repeatedly. It is estimated that alteplase represents between 23% and 32% of thrombolytic drug use in the UK. Alteplase costs £600 per patient (excluding VAT; BNF 43, March 2002).

3.1.7 Reteplase (Rapilysin) is indicated up to 12 hours after symptom onset. It is given as two IV bolus injections 30 minutes apart. It is estimated that reteplase represents between 12% and 15% of thrombolytic drug use in the UK. Reteplase costs £716 per patient (excluding VAT; BNF 43, March 2002).

3.1.8 Tenecteplase (Metalyse) is indicated up to 6 hours after symptom onset. It is administered as a single (weight-adjusted) IV bolus injection. It is estimated that tenecteplase currently accounts for around 1% of thrombolytic drug use in the

UK, the manufacturer indicates that the proportion is increasing. Tenecteplase costs £700 to £770 per patient (excluding VAT; BNF 43, March 2002).

3.2 Delivering thrombolytic drugs

3.2.1 The National Service Framework (NSF) for coronary heart disease (CHD) in England and Tackling CHD in Wales specify that eligible patients with AMI should be given thrombolysis within 60 minutes of calling for professional help ('call-to-needle' time) and should receive thrombolysis within 20 minutes of arriving at hospital ('door-to-needle' time). It is also suggested that it may be appropriate to provide pre-hospital thrombolysis where local 'call-to-hospital' times are likely to be over 30 minutes. The NHS Plan in England gave a commitment to train and equip ambulance paramedics to provide thrombolysis.

3.2.2 Direct admission to a coronary care unit (CCU) is often not possible, and A&E departments are being encouraged to administer thrombolysis to reduce delays in door-to-needle times. The potential for specialist nursing input in the delivery of thrombolysis is being developed.

3.2.3 Given the benefits of early administration of thrombolysis on reducing damage to heart muscle and consequently on long-term outcomes, pre-hospital administration of thrombolysis by ambulance paramedics is being gradually implemented in the NHS.

3.2.4 Currently, pre-hospital thrombolysis is administered by fewer than five ambulance services and a small number of remote community hospitals in England and Wales. Ongoing changes in infrastructure and training will be required to implement the requirements of the NSF for CHD, Tackling CHD in Wales and the NHS Plan to allow more widespread delivery in pre-hospital settings.

3.2.5 Currently, streptokinase is the only thrombolytic that paramedics are authorised to administer under the Prescription Only Medicines (Human Use) Order 1997. However, paramedics can administer other thrombolytic drugs under local Patient Group Directions, and guidelines on their use by paramedics have been developed by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC).

3.2.6 There are practical difficulties in giving controlled-rate infusions in pre-hospital settings, including drug preparation requirements, the practicalities of giving an infusion in an ambulance and, for streptokinase, concerns about higher rates of allergic reactions and hypotension, which are more difficult to manage away from hospital.

3.2.7 Although they are not within the scope of this appraisal, a number of organisational models of service delivery are relevant when considering the feasibility of administering different thrombolytic agents and their effectiveness in particular settings. These involve organisational, practical and operator issues. In-hospital thrombolysis models include:

- assessment and treatment in A&E
- rapid assessment in A&E and transfer to CCU
- direct admission to CCU.

Pre-hospital models include:

- community hospital administration (nurse or general practitioner)
- general practitioner administration (at the point of contact)
- telemetry-supported paramedic administration
- autonomous paramedic administration.

4 Evidence

The appraisal committee reviewed the evidence from a number of sources.

4.1 Clinical effectiveness

4.1.1 In-hospital thrombolysis

4.1.1.1 Fourteen randomised controlled trials (RCTs) comparing thrombolytic drugs were included in the review. Overall the studies were considered to be of excellent quality. In total, the trials involved over 142,000 patients, and 5 of the trials included over 10,000 patients each. The trials had similar inclusion criteria in terms of age (usually less than 70 or 75 years), ECG changes, duration of symptoms, and presentation within 6 hours of symptom onset. Five of the trials included between 12% and 26% of patients aged over 70 to 75 years. Women were under-represented in all of the studies. Primary endpoints included 30-day mortality, 90-minute artery patency/flow rates and left ventricular function. Secondary endpoints included bleeding, stroke, congestive heart failure, reinfarction, allergy and anaphylaxis. The results of the trials were also pooled in a meta-analysis.

4.1.1.2 No direct trial comparisons between tenecteplase and streptokinase or between tenecteplase and reteplase have been undertaken, and only cautious conclusions can be drawn from the indirect comparisons that can be deduced from other studies.

Streptokinase

4.1.1.3 Two placebo-controlled trials were instrumental in establishing the efficacy of streptokinase in reducing mortality. The GISSI trial (published in 1986) included 11,712 patients, and the ISIS-2 trial (published in 1988) included 17,187 patients. In the GISSI study, 21-day mortality was 10.7% in patients treated with streptokinase and 13% in those treated with placebo. This represents a statistically significant absolute reduction of 2.3% (risk ratio 0.81; 95% confidence ratio [CI] 0.72 to 0.9).

In the ISIS-2 study, vascular mortality at 5 weeks was 9.2% in patients treated with streptokinase and 12% in those treated with placebo. This represents a statistically significant absolute reduction of 2.8%. These benefits were independent of those of early aspirin treatment.

Alteplase

4.1.1.4 A meta-analysis of 8 comparisons of standard alteplase with streptokinase found no significant difference between the 2 drugs in terms of mortality up to 35 days (odds ratio 1.0; 95% CI 0.94 to 1.06). A statistically significant difference in reinfarction rates in favour of alteplase was found (odds ratio 0.86; 95% CI 0.77 to 0.95). However, alteplase was associated with a statistically significant higher risk of stroke (odds ratio 1.37; 95% CI 1.16 to 1.62), due to a doubling in the risk of haemorrhagic stroke (odds ratio 2.13; 95% CI 1.04 to 4.36). However, streptokinase was associated with a statistically significant higher risk of major bleeds (other than stroke) than alteplase (odds ratio 0.81; 95% CI 0.68 to 0.97). The categorisation and reporting of major bleeding varied between the trials, so it is difficult to judge the clinical significance of these findings.

4.1.1.5 The studies included in this meta-analysis used the standard alteplase administration regimen, whereas the GUSTO-I trial used the accelerated regimen and is the only trial to have demonstrated superiority between different thrombolytic agents. The GUSTO-I trial included over 40,000 patients. It found an odds ratio of 0.85 (95% CI 0.78 to 0.94) for 30-day mortality for accelerated alteplase compared with streptokinase, and an absolute reduction in mortality at 30 days of 1.0% (6.3% versus 7.3%; 95% CI 0.4% to 1.6%) in favour of accelerated alteplase. However, this benefit was balanced by a statistically significantly higher incidence of haemorrhagic stroke (odds ratio 1.42; 95% CI 1.05 to 1.91). Using a combined outcome measure of mortality and disabling stroke, the absolute advantage of accelerated alteplase over streptokinase was lower (0.9%; p=0.006). Rates of bleeds (moderate or worse), allergic reaction, anaphylaxis, congestive heart failure, and sustained hypotension were statistically significantly lower in the group treated with accelerated alteplase. A further meta-analysis of 9 comparisons of alteplase with streptokinase, including the findings of GUSTO-I (or accelerated alteplase), found no significant difference between the 2 drugs in terms of mortality up to 35 days (odds ratio 0.94; 95% CI 0.85 to 1.04).

Reteplase

4.1.1.6 Reteplase has also been compared with streptokinase in a study involving 5,986 patients (the INJECT study). This study found an absolute difference of 0.5% (95% CI -1.98% to 0.96%) in 35-day mortality in favour of reteplase (not statistically significant). If it is accepted that a 1% difference in mortality is the limit of equivalence in thrombolytic therapy, this suggests that it is unlikely that reteplase is inferior to streptokinase. An alternative interpretation is that in terms of overall effects on mortality and disabling stroke reteplase may be inferior to streptokinase, as the trial also found a statistically significantly lower risk of haemorrhagic stroke (odds ratio 2.1; 95% CI 1.02 to 4.31) in the streptokinase group. However, the trial also found that the rates of heart failure (23.6% vs 26.3%, $p<0.05$) and allergic reactions (1.1% vs 1.8%, $p<0.05$) were statistically significantly lower in the reteplase group.

4.1.1.7 Reteplase has also been compared with accelerated alteplase in 1 relatively small (n=324) study that examined intermediate angiographic endpoints of coronary vessel patency (RAPID-2), and 1 larger study that examined patient-focused endpoints (GUSTO-III, n=15,059). GUSTO-III was designed to test the clinical superiority of reteplase over accelerated alteplase, following the findings in RAPID-2 of better coronary artery patency with reteplase. However, GUSTO-III found no statistically significant difference between the 2 drugs, in terms of survival or adverse effects. The mortality rate at 30 days was 7.5% in the reteplase group and 7.2% in the accelerated alteplase group: an absolute risk reduction of 0.23% in favour of accelerated alteplase (95% CI -1.10% to 0.66%). Given the confidence limits, reteplase cannot be considered as equivalent to accelerated alteplase.

Tenecteplase

4.1.1.8 ASSENT-2, an equivalence trial of over 16,000 patients compared tenecteplase and accelerated alteplase. The study found that 30-day mortality was almost the same in the tenecteplase group (6.2%) and the accelerated alteplase (6.2%) group. The absolute difference of 0.03% in favour of accelerated alteplase was not statistically significant (95% CI -0.55% to 0.61%). Given the confidence limits, tenecteplase and accelerated alteplase can be considered equivalent in terms of mortality. However, there was a small but statistically significant reduction in the

incidence of bleeding with tenecteplase (26.4% compared with 28.9% in the accelerated alteplase group), resulting in fewer blood transfusions in the tenecteplase group (4.3% of patients compared with 5.5% in the accelerated alteplase group). Also, the rate of heart failure was statistically significantly lower in the tenecteplase group than in the accelerated alteplase group (6.1% vs 7.0%, p=0.026).

Subgroups

4.1.1.9 None of the trials discussed was designed to investigate clinical subgroups, such as by age or site of infarct (anterior, inferior). It was concluded that there was no convincing evidence of relative differences in the effectiveness of the available drugs in subgroups. The greater absolute benefit found in patients with anterior infarcts in GUSTO-I may simply be a reflection of the higher baseline risk in this group. The greater relative benefit in patients aged under 75 years was not reflected in their level of absolute risk reduction. None of the differences between the subgroups appeared to be statistically significant by interaction.

Summary

4.1.1.10 In summary, given the evidence on clinical effectiveness, it can be concluded that, in the hospital setting, in terms of mortality:

- standard alteplase is as effective as streptokinase
- reteplase is at least as effective as streptokinase, and
- tenecteplase is as effective as accelerated alteplase.

4.1.1.11 If accelerated alteplase is believed to be superior to streptokinase, then indirectly tenecteplase would also be considered to be superior to streptokinase.

4.1.1.12 Conclusions regarding the equivalence of reteplase compared with accelerated alteplase depend on the interpretation of GUSTO-III.

4.1.1.13 Furthermore, if reteplase is considered to be equivalent to accelerated alteplase,

then this indirectly implies that reteplase is as effective as tenecteplase.

4.1.1.14 Important differences in major adverse events between the thrombolytic agents are also apparent. The newer drugs are associated with a higher risk of haemorrhagic stroke compared with streptokinase, but there are no apparent differences in the frequency of haemorrhagic stroke between accelerated alteplase and reteplase (GUSTO-III), or between accelerated alteplase and tenecteplase (ASSENT-2). However, compared with streptokinase, the newer drugs may also be associated with a lower incidence of congestive heart failure. In addition, allergic reactions are more common with streptokinase than with the other drugs, and major bleeds (leading to transfusions) may also be more common with streptokinase, although the evidence on this is not consistent across the trials. There is also some evidence that tenecteplase may be associated with lower rates of major bleeds and heart failure than accelerated alteplase.

4.1.2 Pre-hospital thrombolysis

4.1.2.1 No RCTs were found comparing the different thrombolytic drugs in pre-hospital settings.

4.1.2.2 However, 9 RCTs and a systematic review investigating the feasibility, safety and efficacy of pre-hospital administration of thrombolysis compared with hospital administration were considered in the context of the appraisal. A number of other papers reporting non-randomised studies and audits of pre-hospital thrombolysis were also considered in relation to practical and implementation issues.

4.1.2.3 The RCTs were small, except for one that included over 5,000 patients (EMIP). They were undertaken in a mixture of urban and/or rural settings in Israel, continental Europe, Canada, the USA, Northern Ireland, and Scotland. A variety of thrombolytic drugs were studied – 4 studies used alteplase, 4 used streptokinase-type drugs, and 1 used urokinase (which is not available in the UK). Only the USA study (MITI) involved paramedics administering the thrombolytic (after remote consultation with a physician). In all but 1 of the other studies, a hospital physician attended the patient and administered the drug. In the rural Scottish trial (GREAT) a general practitioner undertook assessment and

treatment.

4.1.2.4 The RCTs found that, on average, pre-hospital thrombolysis was administered 58 minutes earlier than hospital thrombolysis; the differences ranged from 33 minutes in the MITI study to 130 minutes in the GREAT study. Individually, the trials failed to show statistically significant reductions in in-hospital mortality, although findings in all of the studies favoured pre-hospital administration. However, a meta-analysis of 6 of the trials found a statistically significant absolute reduction in mortality of 1.6% (95% CI 0.2% to 3%), and a relative risk reduction of 17% (95% CI 2% to 30%, p=0.03) favouring pre-hospital administration of thrombolysis. This analysis is heavily influenced by the results of the GREAT study (in which thrombolysis was administered by general practitioners in rural Scotland) and therefore does not directly relate to the potential for paramedic-based pre-hospital thrombolysis.

4.1.2.5 A number of observational studies examining pre-hospital thrombolysis were considered, although these generally only provide further insight into feasibility and safety. They include studies of administration of anistreplase (a streptokinase-like drug that is no longer available in the UK) by paramedics or general practitioners in a Dutch city, reteplase administered by ambulance-based nurses in Sweden, reteplase administered by paramedics in the USA, anistreplase administered in a rural Italian emergency room, and 2 reports of a small number of cases of reteplase administered by paramedics with hospital telemetry support in England.

4.2 Cost effectiveness

4.2.1 In-hospital thrombolysis

4.2.1.1 The assessment group's literature review found 8 published articles on the cost-effectiveness of thrombolytic agents that met the inclusion criteria for the review of cost effectiveness. All compared streptokinase and alteplase (standard and accelerated) in a hospital setting. Three of the articles reported different aspects of the same cost-effectiveness model. Most studies reported incremental costs per life-year gained, and 3 also reported incremental cost per quality-adjusted

life year (QALY). Most of the studies were based on the effectiveness results of GUSTO-I, in which data on resource use were collected only for USA centres. Consequently, the analyses undertaken in Canada, Ireland and France had to attempt to translate these to settings in other countries.

4.2.1.2 In general, the studies had the following limitations: costs and benefits were not measured in the same populations; comparator treatments were often inadequately described; and the derivation of utility values was inadequately explained. None of the studies undertook costing at a patient level and, while in general similar cost categories were included, only some of the studies included the longer-term costs of stroke and heart failure. Some of the studies included consideration of adverse events, including stroke, reinfarction, major bleeds, anaphylaxis, and congestive heart failure.

4.2.1.3 The analyses undertaken following GUSTO-I, which found a survival advantage for accelerated alteplase at 30 days, showed the drug to be cost effective compared with streptokinase within the context of the clinical trial in the US healthcare system. In all of the studies, sensitivity analyses found that assumptions regarding mortality differences and costs were important, so any conclusions drawn are heavily dependent on the interpretation of the effectiveness findings of GUSTO-I.

4.2.1.4 In particular, the economic analysis undertaken in the USA alongside GUSTO-I modelled lifetime costs and benefits, and reported an incremental cost per life-year gained of $32,678 and an incremental cost per QALY of $36,402 for accelerated alteplase compared with streptokinase. The subgroup analyses found that accelerated alteplase became more cost effective in patients with higher absolute mortality risk – for example, $13,410 per life-year gained in patients older than 75 years with anterior myocardial infarction. However, the analysis requires extremely cautious interpretation given a number of issues, including uncertainties over the interpretation of GUSTO-I (in general and in subgroups), application of US data on resource use, and the assumption that costs did not differ significantly between treatment groups.

4.2.1.5 Overall, there is little relevant published evidence on the economics of thrombolytics in a UK setting, and none examining the currently available bolus drugs. However, 2 cost-effectiveness models were submitted by manufacturers.

4.2.1.6 It is logical to assume that the earlier the administration the greater the reduction in damage to the heart. However, while precise assumptions about the survival/time-to-treatment curve affect the benefit results in any modelling, it is unlikely that any one drug has a large advantage over any other with regard to timing of administration.

4.2.1.7 The 2 manufacturers' models are similar in structure and scope, although they differ in terms of method and level of detail. Roche's model examines costs up to 30 days, assumes all 4 drugs have equivalent efficacy, and has less detailed costing. In contrast the Boehringer Ingelheim model includes costing up to 10 years, includes long-term costing for individual complications (such as congestive heart failure and stroke), and incorporates differential survival and complication outcomes for the drugs and more detailed estimation of utilities. Both models incorporate a range of different assumptions regarding adverse events. The models also incorporate adjustment for the timing of administration, including time-savings in pre-hospital settings in which only bolus drugs are compared.

4.2.1.8 The Roche model essentially represents a cost-minimisation analysis, and finds reteplase slightly less costly than accelerated alteplase or tenecteplase in hospital. The Boehringer Ingelheim model assumes better survival and a lower incidence of post-infarct congestive heart failure (streptokinase 15.4%, accelerated alteplase 13.5%, reteplase 13.5%, tenecteplase 11.8%) for tenecteplase. These assumptions, together with 10-year discounted costs, lead to a finding that tenecteplase dominates accelerated alteplase and reteplase in hospital (that is, it is of lower cost and greater effectiveness).

4.2.1.9 The assessment group adjusted key parameters, tested sensitivities and presented revised results using the manufacturers' models. The sensitivity analysis examined the parameter values submitted by the manufacturers for the following: 30-day mortality, strokes, major bleeds, reinfarctions and congestive heart failure.

4.2.1.10 The assessment group used the adjusted models to compare the 3 newer drugs with streptokinase. For each comparison, the additional benefit (using QALYs) of the newer thrombolytic was small, while the additional cost was substantial. The cost differences between the newer drugs are relatively small. The most reliable

finding is that streptokinase is by far the cheapest drug and although it is a little less effective (in terms of discounted QALYs), it is the most cost effective.

4.2.1.11 Using the adjusted manufacturers' models, the incremental costs per QALY reported for the 3 drugs compared with streptokinase were: accelerated alteplase, £7,219 (adjusted Boehringer Ingelheim model) and £7,878 (adjusted Roche model); reteplase, £7,893 and £10,247; and tenecteplase, £8,321 and £9,509. However, these cost–utility rankings of the 3 drugs relative to streptokinase are sensitive to changes in assumptions in the models, and so are not conclusive.

4.2.2 Pre-hospital thrombolysis

4.2.2.1 No published articles examining the cost effectiveness of different thrombolytic drugs in pre-hospital settings were found.

4.2.2.2 There is a published economic analysis of the GREAT study comparing cost effectiveness of pre-hospital and in-hospital thrombolysis (that is, the cost effectiveness of the different drugs), which found that pre-hospital delivery had an incremental cost per life saved of £3,890. The sensitivity analysis found that the cost per life saved could increase to £88,000. It should also be borne in mind that the benefits found in the GREAT trial were larger than those found in other studies, the economic analysis was not undertaken alongside the trial, the interventions were not described in detail, and the model of rural Scottish general practitioner care is unlikely to be applicable throughout the NHS in England and Wales.

4.2.2.3 In the pre-hospital setting, Roche's model assumes that reteplase and tenecteplase have equivalent efficacy and that reteplase is slightly cheaper. The Boehringer Ingelheim model finds that tenecteplase dominates reteplase in pre-hospital settings (that is, it has a lower cost and greater effectiveness).

4.2.2.4 Building on the conclusions about in-hospital cost effectiveness, and since the general pre-hospital delivery costs for the 2 suitable bolus drugs (reteplase and tenecteplase) would be the same, the relative cost effectiveness of the drugs in pre-hospital settings is likely to be similar to that in hospital (assuming equal

effectiveness of both drugs in each setting). On this basis it was concluded that it was not possible to distinguish between reteplase and tenecteplase on grounds of cost effectiveness in pre-hospital settings.

4.3 Consideration of the evidence

4.3.1 In-hospital thrombolysis

4.3.1.1 The committee noted the debate over the applicability of the findings of GUSTO-I beyond the North American centres (where most of the benefit of alteplase over streptokinase was found). The committee considered that the efficacy of accelerated alteplase should not be determined solely from the results of the GUSTO-I trial.

4.3.1.2 Despite concerns over the interpretation of GUSTO-I, the committee concluded that it was likely that the newer thrombolytic agents are more effective than streptokinase in terms of 30-day mortality.

4.3.1.3 The committee was aware of the documented higher rates of stroke associated with the newer agents and carefully considered the views of clinical experts on this issue.

4.3.1.4 The committee considered that differences in the benefit of one thrombolytic agent over another are less clear if the combination of mortality and stroke endpoints are taken into account, particularly for subgroups at higher risk of haemorrhagic stroke. Furthermore, when considering the combination of mortality and stroke endpoints, it could be argued that the differences in overall benefit are less clear, particularly for subgroups at higher risk of developing haemorrhagic stroke.

4.3.1.5 In taking the view that the use of streptokinase is cost effective, the committee concluded that, although the acquisition cost of each of the newer drugs is substantially higher than that of streptokinase, the available economic evidence demonstrates that the newer drugs have an acceptable incremental cost-effectiveness ratio when compared with streptokinase.

4.3.1.6 Given that streptokinase is associated with a lower risk of stroke and is a cost-effective drug, the committee also considered it appropriate that all of the available thrombolytic drugs should be considered as options for use in care pathways for AMI. Local organisational and clinical policy considerations, such as proximity of CCU facilities and A&E staffing, will also have an impact on decisions regarding the appropriate use of each of the drugs in hospital.

4.3.1.7 Because the drugs will have different risk–benefit profiles for individual patients, the committee concluded that the decision about which of the available drugs to use should be made after balancing the likelihood of the benefits and risks (for example, stroke) to which the different drugs would expose the individual.

4.3.1.8 The committee took into account the potential importance of the methods of administration of the different thrombolytics and their effect on door-to-needle times. However, the impact of this factor on reducing myocardial damage and important clinical outcomes was very dependent on the overall pain-to-needle time. Thus, a saving of a few minutes in the door-to-needle time was likely to have a much greater impact on these endpoints where the pain-to-needle time was 1 hour compared with the situation where the pain-to-needle time was 6 hours.

4.3.2 Pre-hospital thrombolysis

4.3.2.1 The committee noted that while there is observational evidence to support pre-hospital thrombolysis, applying the results to the current NHS context is difficult, in that a minority used currently available bolus drugs, most are not paramedic based, and none was reliably generalisable to England and Wales.

4.3.2.2 In the absence of comparative evidence on thrombolytics in pre-hospital settings, the committee considered that the findings of trials comparing different thrombolytic drugs in hospital could still reasonably be applied to pre-hospital settings, with consideration of the additional relevant factors including safety and applicability examined in the pre-hospital studies outlined above.

4.3.2.3 On the basis of advice from experts that only the bolus drugs were appropriate for pre-hospital administration given the practical difficulties explained in section

3.2.6, and given that no high-quality evidence was available to differentiate reteplase and tenecteplase in terms of clinical effectiveness or cost effectiveness in pre-hospital settings, the committee considered that either reteplase or tenecteplase could be used in these settings, provided that the necessary infrastructure and training is provided to fully establish an appropriate model of pre-hospital thrombolytic administration.

4.3.2.4 Given the risks associated with thrombolytic drugs and the fact that pre-hospital administration is an emerging practice in England and Wales, the committee considered it important to ensure high-quality training and supervision of staff involved in the administration of thrombolysis. It was also considered important that clinicians and organisations delivering pre-hospital thrombolysis should develop clear clinical protocols for the use of thrombolytic drugs, such as those developed by the JRCALC, and adopt robust clinical governance arrangements to monitor the use of and outcomes associated with these drugs.

5 Proposed recommendations for further research

5.1 In light of the ongoing introduction of pre-hospital thrombolysis, it is recommended that opportunities for the evaluation of the administration of thrombolytic drugs in pre-hospital settings are explored.

6 Resource impact for the NHS

6.1 Using estimates of the total number of people receiving thrombolysis and the mixture of thrombolytic drugs used, current annual spending on thrombolytic drugs in England and Wales is estimated to be between £13 million and £26 million (drug costs alone, excluding VAT).

6.2 If, as is believed, the current need for thrombolysis is only partly met, and more clinically eligible patients were to receive thrombolytic drugs, cost estimates would be markedly higher.

6.3 It is difficult to predict the local impact of the guidance on the hospital prescribing patterns of available thrombolytic drugs. Consequently, only approximate estimates of the likely NHS resource impact of this guidance can be made, based on possible patterns of hospital prescribing of the alternative available drugs.

6.4 Assuming that the current overall level of thrombolytic therapy remains unchanged, if streptokinase represented 20% of thrombolytic drugs prescribed, alteplase 10%, and reteplase and teneteplase each accounted for 35%, then the total annual spending on thrombolytic drugs in England and Wales would be between £27 million and £45 million. If these levels were assumed to be 35%, 20% and 22.5% respectively, then the total would be between £22 million and £36 million.

6.5 In addition, substantial costs are associated with the introduction of pre-hospital thrombolysis. These include the costs of additional equipment, training, and potentially longer ambulance time spent treating patients with AMI. Also, any expansion of pre-hospital thrombolysis would result in a shift of drug costs from acute hospital trusts to other services such as ambulance trusts or primary care trusts and, potentially, result in an increase in total local spending on thrombolytic drugs where bolus drugs were not widely used in hospital. Such costs are difficult to estimate usefully on the basis of the information available to NICE at the time of this appraisal.

7 Implementation

7.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

7.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

7.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has acute myocardial infarction and the healthcare professional responsible for their care thinks that alteplase, reteplase, streptokinase or tenecteplase are the right treatment, they should be available for use, in line with NICE's recommendations.

8 Appraisal committee members

The appraisal committee is a standing advisory committee of NICE. Its members are appointed for a 3-year term. A list of the committee members who took part in the discussions for this appraisal appears below. The appraisal committee meets 3 times a month except in December, when there are no meetings. The committee membership is split into 3 branches, with the chair, vice-chair and a number of other members between them attending meetings of all branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St. George's Hospital, London

Professor RL Akehurst
Dean, School of Health Related Research, Sheffield University

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology, University of Leicester

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Carol Black
Consultant Physician, Royal Free Hospital & UCL, London

Professor John Brazier
Health Economist, University of Sheffield

Professor Martin Buxton
Director of Health Economics Research Group, Brunel University

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Karl Claxton
Health Economist, University of York

Professor Sarah Cowley
Professor of Community Practice Development, Kings College, London

Professor Jack Dowie
Health Economist, London School of Hygiene & Tropical Medicine, London

Mr Chris Evennett
Chief Executive, Mid-Hampshire Primary Care Group

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust

Professor Terry Feest
Clinical Director and Consultant Nephrologist, Richard Bright Renal Unit, and Chairman of the UK Renal Registry

Professor Gary A Ford
Professor of Pharmacology of Old Age/ Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust

Mrs Sue Gallagher
Chief Executive, Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline

Sally Gooch
Director of Nursing, Mid-Essex Hospital Services Trust

Mr John Goulston
Director of Finance, The Royal Free Hampstead NHS Trust

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London

Miss Linda Hands
Consultant Vascular Surgeon, John Radcliffe Hospital, Oxford

Professor Philip Home
Professor of Diabetes Medicine, University of Newcastle

Dr Terry John
General Practitioner, The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader, NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester, and Lecturer, University of Leicester

Ruth Lesirge
Lay Representative; Director, Mental Health Foundation

Dr George Levvy
Lay Representative; Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
CEO, North & East Devon Health Authority

Professor Miranda Mugford
Health Economist, University of East Anglia

Mr M Mughal
Consultant Surgeon, Chorley and South Ribble NHS Trust

Mr James Partridge
Lay Representative; Chief Executive, Changing Faces

Siân Richards
General Manager, Cardiff Local Health Group

Professor Philip Routledge
Professor of Clinical Pharmacology, University of Wales College of Medicine

Dr Rhiannon Rowsell
Pharmaceutical Physician, AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Professor Andrew Stevens (Vice-chairman)
Professor of Public Health, University of Birmingham

Professor Ray Tallis
Consultant Physician, Hope Hospital, Salford

Dr Cathryn Thomas
General Practitioner, and Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Professor Mary Watkins
Head of Institute of Health Studies, University of Plymouth

Dr Norman Waugh
Public Health Consultant, University of Southampton

9 Sources of evidence considered by the committee

The following documentation and opinion were made available to the committee:

Assessment report prepared by the Liverpool Reviews and Implementation Group, Department of Pharmacology and Therapeutics, University of Liverpool: Early Thrombolysis for the Treatment of Acute Myocardial Infarction, April 2002.

Manufacturer or sponsor submissions:

- Aventis Behring
- Boehringer Ingelheim
- Roche

Professional or specialist and patient or carer group submissions:

- British Association for Immediate Care
- British Association for Nursing in Cardiac Care
- British Heart Foundation
- Faculty of Accident & Emergency Medicine and British Association of Accident and Emergency Medicine
- Faculty of Pre-Hospital Care, Royal College of Surgeons, Edinburgh
- Joint Royal Colleges Ambulance Liaison Committee and Ambulance Service Association
- Primary Care Cardiovascular Society
- Royal College of Physicians and British Cardiac Society
- Warwickshire Health Authority
- Welsh Ambulance Services NHS Trust

Expert perspectives:

- Professor Douglas Chamberlain, Chairman, Joint Royal Colleges Ambulance Liaison Committee
- Mr Andrew Marsden, Consultant Medical Director, Scottish Ambulance Service
- Professor Richard Vincent, Consultant Cardiologist and Professor of Medicine, Trafford Centre for Medical Research

Update information

Minor changes since publication

March 2014: Implementation section updated to clarify that thrombolytic drugs are recommended as an option for treating acute myocardial infarction.

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